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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,785	10/27/2003	Egisto Boschetti	9676-314-999	1038

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EXAMINER
JONES, DAMERON LEVEST

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 10/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/692,785	BOSCHETTI, EGISTO	
	Examiner	Art Unit	
	D. L. Jones	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/2/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-11,15-21,56-60 and 63-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-11, 15-21, 56-60, and 63-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

WITHDRAWAL OF FINALITY

1. The finality of the rejection of the last Office action is WITHDRAWN.

ACKNOWLEDGMENTS

2. The Examiner acknowledges receipt of the amendment filed 10/2/06 wherein claims 1 and 11 are amended; claims 2, 3, 12-14, 22-55, 61, and 62 are canceled; and claims 63-68 are added.

Note: Claims 1, 4-11, 15-21, 56-60, and 63-68 are pending.

CLARIFICATION OF THE RECORD

3. Re-evaluation of the prior art and the pending claims deemed it necessary to place the following rejections on record.

RESPONSE TO APPLICANT'S ARGUMENTS/AMENDMENT

4. The outstanding rejections are MOOT in view of the new grounds of rejection below.

Note: It should be noted that while the claims have been amended to disclose that the aldehydes on the microspheres are neutralized, Bachtis et al (J. Microencapsulation, 1995, Vol. 12, No. 1, pp. 23-35) disclose the use of NaOH which is a neutralizing agent. Thus, since Bachtis et al disclose a PVC (polyvinylalchol) solution having gluteraldehyde added to the mixture, and later the addition of NaOH, it would be obvious to one of ordinary skill in the art that the aldehydes on the microspheres are neutralized.

NEW GROUNDS OF REJECTION

103 Rejections

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 4-6, 11, 15-18, and 56-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bachtis et al (J. Microencapsulation, 1995, Vol. 12, No. 1, pp. 23-35).

Bachtsi et al disclose an experimental investigation of enzyme release from polyvinyl alcohol (PVA) crosslinked microspheres. The spherical crosslinked particles range in size from 30 to 80 microns. The crosslinked particles, after washing and drying, were placed into a protease enzyme solution for loading (see entire document, especially, abstract; page 25-26, 'Particle preparation'; page 27, first complete paragraph). The use of crosslinked PVA hydrogel matrices may be used as delivery systems. The release of drugs from the crosslinked swellable natural polymer matrices (i.e., albumin and gelatin) has been investigated by others in the art (page 24, first complete paragraph). In Table 1 on page 28, enzyme loading into a hydrogel PVA particle having various percentages of PVA crosslinking is disclosed. The percentages include 1, 3, 5, 10, and 20%. Bachtsi et al fail to specifically disclose that the microspheres that they generated are sterile. Furthermore, page 25 of Bachtis et al discloses the particle preparation. In particular, the crosslinking of the PVA was accomplished by the addition of glutaraldehyde into the PVA solution. The aqueous

PVA solution was mixed with a methanol solution, an acetic acid solution, and a sulfuric acid solution. Subsequently a known quantity of 25% glutaraldehyde solution was added to the PVA solution to obtain the desired degree of crosslinking. Eventually, the particles were collected by decantation of the oil phase and gravity filtration. The product was washed several times with acetone to remove the excess oil from the surface of the particle. The dehydrated particles were subsequently suspended in a ***NaOH*** buffer solution (pH 8-9) overnight to remove any unreacted chemicals. ***The crosslinked particles were then washed several times with distilled water until the pH of the washing medium reached a value of 7***. Finally, the particles were dried in an oven at 70 degrees Celsius. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Bachtsi et al and generate sterile microspheres crosslinked PVA, having a diameter within the range of 10 micrometers to about 2,000 micrometers, in the form of a powder wherein the aldehydes on the microspheres are neutralized because Bachtsi et al disclose crosslinked PVA microspheres that meet the limitations of the instant invention based on the diameter, powder form and sterility of the microspheres. The neutralized aldehydes attached to the microspheres are obvious because based on the procedure of generating the microspheres of the prior art, Bachtsi et al disclose that the particles were suspended in NaOH buffer and washed several times with distilled water such that a neutral pH was obtained. As a result, a skilled practitioner in the art would recognize that NaOH acts as a neutralizing agent. It should be noted that in support of the Examiner's position, the definition of sodium hydroxide (NaOH) from Hawley's 12th

Edition, 1993, Condensed Chemical Dictionary by Richard J. Lewis, Sr. pages 1058-1059, is included with this office action. In particular, in the section directed to the possible uses of sodium hydroxide, it is disclosed that one of its uses is as a neutralizing agent in petroleum refining. Furthermore, a skilled practitioner in the art would recognize that since the microspheres of Bachtsi et al are used for pharmaceutical purposes, the NaOH would be used have the same purposes in a sterile environment (i.e., neutralizing a solution) as it would in neutralizing a solution in petroleum refining.

Also, since Applicant has product claims which do not contain an additional agent, e.g., a neutralizing agent, then the cited prior art would inherently result in the aldehydes on the microsphere being neutralized since the components of the microspheres of the instant invention and prior art are the same and a product is inseparable from its properties.

7. Claims 1, 4, 5, 8-11, 15-17, 19-21, 56-60, and 63-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bachtis et al (J. Microencapsulation, 1995, Vol. 12, No. 1, pp. 23-35) in view of Tarara et al (US Patent No. 6,565,885).

Tarara et al disclose pharmaceutical compositions comprising microstructure powders. The microstructures incorporate at least one active agent which may be a bioactive agent. Preferred microstructures are microspheres (see entire document, especially, abstract; column 4, lines 38-46). In addition, Tarara et al disclose that particles having relatively large geometric diameters (i.e., diameters greater than 10

micrometers) are used to reduce the amount of particle interactions which preserves the flowability of the powder (column 3, lines 5-9). The microstructure may comprise fluorochemicals (e.g., perfluorocarbons or fluorocarbons) [column 6, lines 10-26]. The dry powder may contain a bioactive agent such as antineoplastics, imaging agents, steroids, proteins, peptides, antiinflammatories, mast cell inhibitors, cardiovascular agents, enzymes, and combinations thereof. The bioactive agent may be incorporated, blended in coated on, or otherwise associated with the perforated microstructure (column 6, lines 27-52; columns 12-13, bridging paragraph; column 13, lines 48-63). The structural matrix defining the perforated microstructure optionally comprises synthetic or natural polymers or combination thereof. The polymers may comprise ***polyvinyl alcohols*** as well as acrylic copolymers such as styrene-acrylonitrile, ethylene-acrylate, ethylene-acrylic acid, ethylene-methylacryalate, ethylene-ethyl acrylate, vinyl methyl methacrylate, and acrylic acid-methyl (columns 11-12, bridging paragraph) methacrylate. Furthermore, Tarara et al disclose that a primary emulsion may be generated containing polyvinyl alcohol and the resulting microspheres are eventually washed, filtered, and dried prior to combining them with another medium (column 22, lines 40-52). The mean geometric particle sized of the microstructure is preferably about 0.5 to 50 micrometers (columns 22-23, bridging paragraph). The microstructure powder may be used for pulmonary purposed by converting the powder into an aerosol. The3 aerosol is a gaseous suspension of the fine solid or liquid particles. Thus an aerosol or aerolized medicament (i.e., dry powder inhaler, a metered

dose inhaler, an atomizer, or a nebulizer) may be generated (columns 6-7, bridging paragraph).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to generate microspheres having various adhesion promoters, marking agent, and anti-angiogenic agents because Tarara et al disclose microspheres which may contain polyvinyl alcohol that may also contain fluorochemicals, imaging agents, various cell adhesion promoters (i.e., enzymes, peptides, polynucleotides, etc.), and anti-angiogenic agents (i.e., steroids, peptides, proteins, etc). In regards to the aldehydes on the microsphere being neutralized, such property would be inherent to the microspheres generated by Tarara et al because both Applicant and Tarara et al disclose the same microspheres and components thereof. Thus, a skilled practitioner in the art would recognize that a product is inseparable from its properties. As a result, the properties of the microspheres of Applicant would also be the same properties that the microspheres of Tarara et al possess.

8. Claims 1, 4-6, 11, 15-18, 56-60, and 63-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bachtis et al (J. Microencapsulation, 1995, Vol. 12, No. 1, pp. 23-35) in view of Tarara et al (US Patent No. 6,565,885).

Bachtis et al (see discussion above) fail to disclose various types of cell adhesion promoters, marking agents, and anti-angiogenic agents that are useful in combination with microspheres.

Tarara et al (see discussion above) is cited for its teachings directed to cell adhesion promoters, marking agents, and anti-angiogenic agents.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Bachtis et al using the teachings of Tarara et al and generate microspheres having various adhesion promoters, marking agent, and anti-angiogenic agents because Tarara et al disclose microspheres which may contain polyvinyl alcohol that may also contain fluorochemicals, imaging agents, various cell adhesion promoters (i.e., enzymes, peptides, polynucleotides, etc.), and anti-angiogenic agents (i.e., steroids, peptides, proteins, etc). Thus, it would have been obvious to use various cell adhesion promoters, marking agents, and anti-angiogenic agents in combination with the microspheres of Bachtis et al. Furthermore, a skilled practitioner in the art would recognize that since both Tarara et al and Bachtis et al disclose microspheres that comprise polyvinyl alcohol, the references may be considered to be within the same field of endeavor. As a result, the reference teachings are combinable.

9. Claims 1, 4-11, 15-21, 56-60, and 63-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boschetti et al (US Patent No. 5,635,215) in view of Tarara et al (US Patent No. 6,565,885).

Boschetti et al disclose microspheres useful for therapeutic vascular occlusions and injectable solutions containing the same wherein the microsphere has a diameter ranging between 10 to about 2000 micrometers, contains a cell adhesion promoter,

marking agent, and a hydrophilic acrylic copolymer (see entire document, especially, abstract; columns 7-8, claims 1-12). However, Boschetti et al does not disclose a microsphere wherein the polymer is polyvinyl alcohol or specifically state that the aldehydes on the microsphere are neutralized. In addition, Boschetti et al do not disclose that anti-angiogenic agents are used with their microspheres.

Tarara et al (see discussion above).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Boschetti et al using the teachings of Tarara et al and generate a microsphere comprising polyvinyl alcohol, a marking agent, and/or a cell adhesion promoter because the microspheres of Boschetti et al differ from those of the instant invention in that they use an acrylic acid copolymer instead of polyvinylalchol. However, Tarara et al disclose microspheres that may comprise polyvinyl alcohol and teach that polyvinyl alcohol and acrylic acid copolymers are equivalent microsphere structures. Thus, a skilled practitioner in the art would be motivated to replace one polymer/copolymer with another polymer/copolymer of Tarara et al because the reference disclose that both polymers may be used in the formation of microsphere structure. Thus, a skilled practitioner in the art would not expect the overall properties of the microspheres to drastically change by replacing an acrylic polymer with polyvinyl alcohol. In regards to the aldehydes on the microsphere being neutralized, such property would be inherent to the microspheres generated by the prior art and Applicant because since the same microspheres and components thereof are utilized, a skilled practitioner in the art would recognize that a product is inseparable from its

properties. As a result, the properties of the microspheres of Applicant would also be the same properties that the microspheres of the prior art. Furthermore, the incorporation of anti-angiogenic agents would be obvious with the microspheres because Tarara et al disclose various anti-angiogenic agents that may be used in combination with microspheres. Thus, the incorporation of anti-angiogenic agents into microspheres is known in the art.

10. Claims 1, 4-11, 15-21, 56-60, and 63-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boschetti et al (US Patent No. 5,635,215) in view of Tarara et al (US Patent No. 6,565,885).

Boschetti et al disclose microspheres useful for therapeutic vascular occlusions and injectable solutions containing the same wherein the microsphere has a diameter ranging between 10 to about 2000 micrometers, contains a cell adhesion promoter, marking agent, and a hydrophilic acrylic copolymer (see entire document, especially, abstract; columns 7, 8, and 10, claims 1-5, 11-16, and 19). However, Boschetti et al does not disclose a microsphere wherein the polymer is polyvinyl alcohol or specifically state that the aldehydes on the microsphere are neutralized. In addition, Boschetti et al do not disclose that anti-angiogenic agents are used with their invention.

Tarara et al (see discussion above).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Boschetti et al using the teachings of Tarara et al and generate a microsphere comprising polyvinyl alcohol, a marking agent,

and/or a cell adhesion promoter because the microspheres of Boschetti et al differ from those of the instant invention in that they use an acrylic acid copolymer instead of polyvinylalchol. However, Tarara et al disclose microspheres that may comprise polyvinyl alcohol and teach that polyvinyl alcohol and acrylic acid copolymers are equivalent microsphere structures. Thus, a skilled practitioner in the art would be motivated to replace one polymer/copolymer with another polymer/copolymer of Tarara et al because the reference disclose that both polymers may be used in the formation of microsphere structure. Thus, a skilled practitioner in the art would not expect the overall properties of the microspheres to drastically change by replacing an acrylic polymer with polyvinyl alcohol. In regards to the aldehydes on the microsphere being neutralized, such property would be inherent to the microspheres generated by the prior art and Applicant because since the same microspheres and components thereof are utilized, a skilled practitioner in the art would recognize that a product is inseparable from its properties. As a result, the properties of the microspheres of Applicant would also be the same properties that the microspheres of the prior art. Furthermore, the incorporation of anti-angiogenic agents would be obvious with the microspheres because Tarara et al disclose various anti-angiogenic agents that may be used in combination with microspheres. Thus, the incorporation of anti-angiogenic agents into microspheres is known in the art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (571) 272-0617. The examiner can normally be reached on Mon.-Fri., 6:45 a.m. - 3:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D. L. Jones
Primary Examiner
Art Unit 1618

October 26, 2006